

Valaciclovir Compared with Acyclovir for Improved Therapy for Herpes Zoster in Immunocompetent Adults

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Acyclovir treatment of acute herpes zoster speeds rash healing and decreases pain and ocular complications. The limited oral bioavailability of acyclovir necessitates frequent dosing. Valaciclovir, the *L*-valyl ester of acyclovir, is rapidly and almost completely converted to acyclovir in vivo and gives three- to fivefold increases in acyclovir bioavailability. In a randomized, double-blind, multicenter study, the safety and efficacy of oral valaciclovir given at a dosage of 1,000 mg three times daily for 7 or 14 days and oral acyclovir given at a dosage of 800 mg five times daily for 7 days were compared in immunocompetent adults aged ≥ 50 years with herpes zoster. Patients were evaluated for 6 months. The intent-to-treat analysis (1,141 patients) showed that valaciclovir for 7 or 14 days significantly accelerated the resolution of herpes zoster-associated pain ($P = 0.001$ and $P = 0.03$, respectively) compared with acyclovir; median pain durations were 38 and 44 days, respectively, versus 51 days for acyclovir. Treatment with valaciclovir also significantly reduced the duration of postherpetic neuralgia and decreased the proportion of patients with pain persisting for 6 months (19.3 versus 25.7%). However, there were no differences between treatments in pain intensity or quality-of-life measures. Cutaneous manifestations resolved at similar rates in all groups. Adverse events were similar in nature and prevalence among groups, and no clinically important changes occurred in hematology or clinical chemistry parameters. Thus, in the management of immunocompetent patients ≥ 50 years of age with localized herpes zoster, valaciclovir given at 1,000 mg three times daily for 7 days accelerates the resolution of pain and offers simpler dosing, while it maintains the favorable safety profile of acyclovir.

Herpes zoster remains an important medical problem throughout the world. The characteristic rash and associated pain occur when varicella-zoster virus, which becomes dormant in sensory ganglia following primary varicella-zoster virus infection, is reactivated, often in association with declining cellular immunity associated with advancing age (4). Thus, in otherwise healthy adults, the risk of herpes zoster increases with age (12). Pain persisting after rash healing occurs in more than 50% of untreated patients and is the major complication in older adults (3, 13). The pain is often accompanied by abnormal sensations such as allodynia, tingling, or numbness and decreases gradually over several months in most patients (2), although some patients have pain persisting beyond 6 months (8, 13, 20).

Acyclovir (Zovirax) administered orally (800 mg five times daily) is widely used for treatment of acute herpes zoster. It speeds rash healing and decreases the severity of acute pain (14, 18, 25, 28). In some studies, acyclovir also appears to reduce the prevalence, severity, and duration of chronic pain (7, 11, 14, 18). Furthermore, oral acyclovir reduces the prevalence and severity of certain intraocular complications associated with herpes zoster ophthalmicus (5, 11). The limited efficacies of lower oral doses of acyclovir (400 or 600 mg five

times daily) relative to that of the standard dose suggests that efficacy is related to higher acyclovir concentrations in plasma or tissue (5, 14). Thus, achievement of higher concentrations than are attained with the standard oral acyclovir regimen could result in improved benefit, particularly for pain outcome (26). In addition, simpler dosing could improve compliance and minimize the potential for suboptimal treatment of herpes zoster.

Valaciclovir (Valtrex), the *L*-valyl ester of acyclovir, is rapidly converted to acyclovir after oral administration and results in acyclovir bioavailability three to five times greater than that of oral acyclovir in humans (23, 24). Pharmacokinetic modeling predicted that plasma acyclovir concentrations after oral administration of valaciclovir at 1,000 mg three times daily would remain in excess of the in vitro inhibitory concentration for most clinical isolates of varicella-zoster virus (0.12 to 4.0 $\mu\text{g/ml}$ or 0.5 to 17.6 μM) throughout the dosage interval (6, 24). Biotransformation of valaciclovir to acyclovir is virtually complete after oral administration, with each gram of valaciclovir yielding approximately 700 mg of acyclovir and 300 mg of the essential amino acid valine. On the basis of this and preclinical studies, it was anticipated that the established safety profile of acyclovir (21) would be retained with valaciclovir.

The randomized, double-blind, multicenter study described here compared the safety and efficacy of oral valaciclovir and standard oral acyclovir for the treatment of herpes zoster in immunocompetent adults. Both 7- and 14-day valaciclovir regimens were evaluated because, at the time that the study commenced, the optimal duration of antiviral treatment for maximum benefit against pain associated with herpes zoster had not been established.

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MATERIALS AND METHODS

Patients. Patients 50 years of age or older with clinically diagnosed, localized herpes zoster presenting within 72 h after the onset of rash were enrolled in the multicenter, randomized, three-arm, double-blind, double-dummy study described here. The clinical diagnosis of herpes zoster was based on the presence of the unilateral dermatomal rash. The study was predominantly outpatient based, although hospitalized patients were eligible. Patients with herpes zoster ophthalmicus (cutaneous lesions involving the ophthalmic branch of the trigeminal nerve, with or without ocular involvement) were included, and therefore, a placebo regimen could not be considered. Pregnant, nursing, and sexually active women of childbearing potential were excluded, as were patients treated with other antiviral medications, immunomodulating agents, or capsaicin within the previous 4 weeks or those receiving probenecid or tricyclic antidepressant medications at the time of entry. Also excluded were patients with congenital, acquired, or steroid-induced immunodeficiency, including malignancy; impaired renal function (estimated creatinine clearance of ≤ 35 ml/min or serum creatinine of ≥ 120 $\mu\text{mol/liter}$) or impaired hepatic function (either alanine aminotransferase or aspartate aminotransferase level more than threefold the upper limit of normal at the time of entry); or gastrointestinal dysfunction that might interfere with drug absorption. Written informed consent was obtained from each patient.

Drug administration. Patients were randomized (1:1:1) according to a computer-generated code to receive treatment with valaciclovir at 1,000 mg three times daily for 7 days, valaciclovir at 1,000 mg three times daily for 14 days, or acyclovir at 800 mg five times daily for 7 days. All patients received study medication for 14 days. Patients randomized to 7 days of treatment with valaciclovir or acyclovir received placebo during days 8 to 14.

Efficacy assessments. The primary efficacy endpoints were time to the complete cessation of pain, time to cessation of new lesion formation and/or increase in lesion area, and time to $\geq 50\%$ crusting or healed rash (the time by which 50% or more of the rash had crusted over or healed completely). Secondary endpoints included time to the cessation of abnormal sensations, pain intensity, unpleasantness, analgesic use, quality of life, and the impact of pain on daily activities.

Cutaneous assessments were performed by the investigator on days 1 to 7, 10, 14, and 21 and included the determination of new lesion formation and/or an increase in lesion area; the proportion of the rash present as macules or papules, vesicles, crusts, or healed rash; and evidence of dissemination. The occurrence of any complications of herpes zoster was also noted.

To evaluate pain, patients kept a diary to record daily (days 1 to 30) and then weekly (to week 24) assessments of the severity of pain or burning and abnormal sensations such as allodynia, paresthesia, dysesthesia, or hyperesthesia. Patients were defined as achieving complete cessation of pain if they were pain-free for at least 28 days and had no subsequent recurrence of pain during the 24-week observation period. Pain severity and unpleasantness were scored in native English-speaking subjects by using the Gracely scales (9, 10). The impact of pain on daily activities was determined in all patients by using a six-point scale (0 = no pain or discomfort, 1 = pain can easily be ignored, 2 = pain does not interfere with daily activities, 3 = pain interferes with concentration or sleep, 4 = pain interferes with all but basic needs, 5 = pain requires rest or bed rest). Use of medications to control pain, including analgesics and antidepressants, was recorded at each assessment. Unit dose equivalents of opioids plus aspirin plus acetaminophen were calculated (18). Quality of life was further assessed by using part 1 of the Nottingham Health Profile (16), which patients completed on days 1, 14, and 30 and then monthly to week 24.

Safety assessment. All adverse experiences reported during the treatment phase were categorized by COSTART term, intensity, seriousness, and causality. All adverse experiences considered serious were also recorded throughout the follow-up. On days 1, 7, and 14, blood was obtained for blood chemistry and hematology and urine was obtained for protein determination. An additional serum creatinine level determination was performed on day 3.

Plasma acyclovir level monitoring and pharmacokinetic analysis. Blood samples for the determination of plasma acyclovir concentrations at steady state were obtained on days 3, 7, and 14. The time at which each sample was collected in relation to the time of administration of the previous dose of valaciclovir or acyclovir was recorded. Acyclovir concentrations were measured by radioimmunoassay (19), and mean values for subjects in each group were plotted as a function of time. Plasma acyclovir levels for the valaciclovir (pooled) and acyclovir groups were analyzed by using nonlinear mixed-effect modeling (NONMEM version 4 [1]) to estimate acyclovir concentration-time profiles.

Statistical analysis. All analyses were conducted by using Statistical Analysis Systems software (SAS Institute, Inc., Cary, N.C.). The principal analysis was the intent to treat for all efficacy endpoints and for safety.

The distribution of each time-to-event efficacy endpoint was estimated by the Kaplan-Meier product limit survival method. Differences between treatments were determined by using Cox's proportional hazards models. The proportions of patients with pain at 6 months were compared by using Kaplan-Meier estimates of the proportions and corresponding standard errors. For most secondary endpoints, point estimates and their associated 95% confidence intervals (CIs) were derived. Because there is no universally accepted definition of postherpetic neuralgia, the duration of postherpetic neuralgia was evaluated by using two definitions: pain that persisted after rash healing and pain that persisted for more

than 30 days from the time of enrollment. For analyses of postherpetic neuralgia, patients who did not develop postherpetic neuralgia were assigned a duration of postherpetic neuralgia equal to 0 days. This retains some principles of an intent-to-treat analysis and avoids the introduction of bias inherent in a subset analysis. Analysis of cessation of pain after rash healing depends on both the time of pain cessation and the time of rash healing, and treatment may affect both of these parameters, thus confounding the analysis.

Covariates that were fitted to Cox's proportional hazards models to determine differences between treatments for each primary efficacy endpoint included the time from rash onset to treatment initiation (≤ 48 versus 48 to 72 h) and patient age (50 to 60 versus > 60 years). For the time to complete cessation of pain and postherpetic neuralgia, prodromal pain (absence versus presence), pain severity at presentation, and gender were also included in the intent-to-treat analysis. Pain severity at presentation was derived from scores for the impact of pain on daily activities on day 1 (1 = very mild pain, 2 = mild pain, 3 = moderate pain, 4 or 5 = severe pain).

A sample size of 350 patients per treatment group is sufficient to detect differences between treatments in the time to cessation of new lesion formation or no increase in lesion area. It provides 80% power at the 5% significance level to detect the difference between 0.3 and 0.4 in the proportion of patients still forming new lesions after day 2. This difference is equivalent to detecting a hazard ratio of ≤ 0.76 or ≥ 1.31 . This sample size is also sufficient to detect similar treatment differences in time to $\geq 50\%$ crusting or healed rash and the time to complete cessation of pain.

RESULTS

Patients. A total of 1,141 patients were enrolled at 107 study centers in 13 countries. Overall, 384 patients were randomized to treatment with valaciclovir for 7 days, 381 were randomized to treatment with valaciclovir for 14 days, and 376 were randomized to treatment with acyclovir for 7 days. All 1,141 enrolled patients were included in the intent-to-treat analysis. Of these, 946 (82.9%) completed the 24-week study according to the study protocol. Of the 195 patients who did not complete the study as planned, the most common reasons were protocol violation (71 patients), adverse experiences (38 patients), withdrawal of consent (30 patients), and loss to follow-up (24 patients); the reasons were similarly distributed across the three treatment groups. All 1,138 patients for whom data on pain were available were included in the intent-to-treat analysis of pain endpoints.

Demographic and baseline characteristics were similar in all three treatment groups (Table 1). Overall, there were 648 females (56.8%) and 493 males (43.2%), mostly white (94.7%) and ranging in age from 49 to 99 years (mean, 68 years). Approximately 60% of patients presented within 48 h of the appearance of the herpes zoster rash; the proportion was comparable in all treatment groups. The proportions of patients reporting prodromal pain ($> 80\%$) and the severity of pain at presentation were also similar in the three groups.

Thirty-one patients with no prior history of renal impairment commenced treatment but were subsequently found to have had low estimated creatinine clearance and elevated serum creatinine values at presentation. In 22 patients, treatment with the study medication was stopped prematurely when evidence of renal impairment at presentation became known. The remaining nine patients (creatinine clearance, 20 to 35 ml/min; serum creatinine level, 124 to 194 $\mu\text{mol/liter}$) completed the treatment course. All 31 patients were included in all safety and efficacy analyses.

Herpes zoster-associated pain. The intent-to-treat analysis of all herpes zoster-associated pain, which includes acute pain and postherpetic neuralgia, revealed that valaciclovir treatment for 7 or 14 days significantly accelerated the resolution of pain ($P = 0.001$ and $P = 0.03$, respectively) compared with acyclovir treatment. The median time to the cessation of pain was shorter in the 7- and 14-day valaciclovir groups at 38 and 44 days, respectively, than in the acyclovir group (51 days) (Fig. 1). No further advantage was conferred by treatment with valaciclovir for 14 days compared with treatment for 7 days.

TABLE 1. Patient demographic characteristics by treatment group

Characteristic	Valaciclovir, 7 day (<i>n</i> = 384)	Valaciclovir, 14 day (<i>n</i> = 381)	Acyclovir (<i>n</i> = 376)
Sex (no. of males/no. of females)	155/229	194/187	144/232
Age (yr), mean (range)	69 (49–93) ^a	68 (50–99)	68 (50–98)
Race (no. [%])			
White	362 (94.3)	364 (95.5)	354 (94.1)
Black	13 (3.4)	10 (2.6)	12 (3.2)
Other	9 (2.3)	7 (1.8)	10 (2.7)
Herpes zoster ophthalmicus (no. [%])			
Present	35 (9.1)	46 (12.1)	38 (10.1)
Absent	349 (90.9)	335 (87.9)	338 (89.9)
Prodrome (no. [%])			
Present	314 (81.8)	313 (82.2)	310 (82.4)
Absent	70 (18.2)	67 (17.6)	66 (17.6)
Missing	0	1 (0.3)	0
Pain at presentation (no. [%])			
Very mild	81 (21.1)	88 (23.1)	84 (22.3)
Mild	79 (20.6)	84 (22.0)	86 (22.9)
Moderate	173 (45.1)	167 (43.8)	154 (41.0)
Severe	49 (12.8)	39 (10.2)	49 (13.0)
Missing	2 (0.5)	3 (0.8)	3 (0.8)

^a One patient age 49 years was inadvertently enrolled in the study.

The hazard ratios (CIs) for the resolution of pain for each treatment group comparison are listed in Table 2 and demonstrate that with valaciclovir, pain cessation is on average up to 34% faster than that with acyclovir. Kaplan-Meier estimates indicated that a higher proportion of patients in the acyclovir group (25.7%) still experienced pain at the end of the study (week 24) compared with the proportion in the group receiving valaciclovir for 7 days (19.9%; $P = 0.08$) or the group receiving

valaciclovir for 14 days (18.6%; $P = 0.03$). Overall, the estimated proportion of patients with pain at the end of the study in patients treated with valaciclovir (19.3%) was significantly lower than that of patients treated with acyclovir ($P = 0.02$).

Factors influencing pain. Cox's proportional hazards models showed that age, the presence of prodromal pain, and the presence of more severe pain at presentation were all important factors that predisposed the patient to a longer pain du-

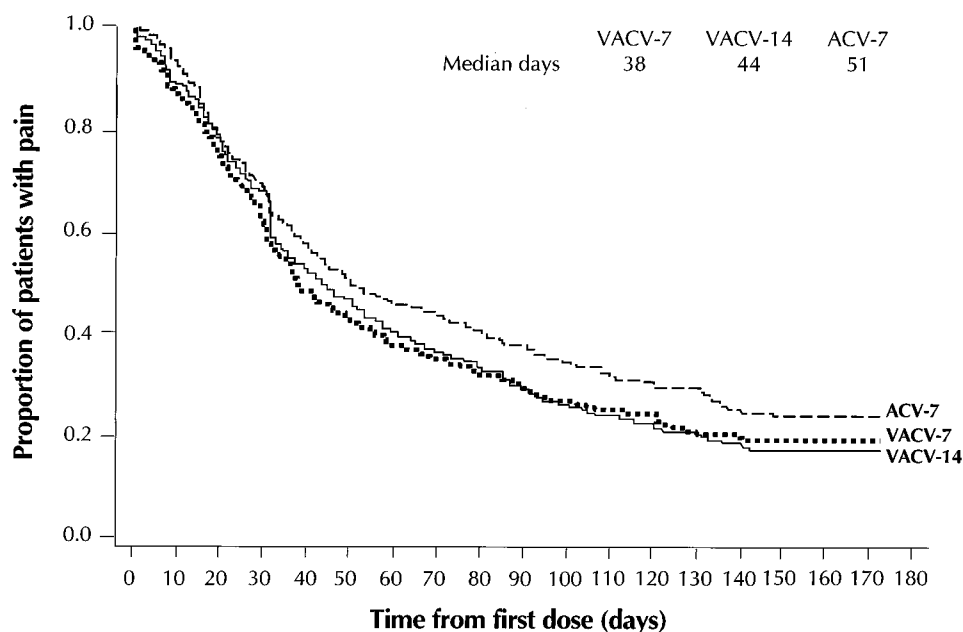


FIG. 1. Kaplan-Meier curves of the time to cessation of pain (intent-to-treat analysis) in patients with herpes zoster treated with oral valaciclovir or oral acyclovir. VACV-7, valaciclovir at 1,000 mg three times daily for 7 days; VACV-14, valaciclovir at 1,000 mg three times daily for 14 days; ACV-7, acyclovir at 800 mg five times daily for 7 days.

TABLE 2. Hazard ratios (CIs) for key efficacy parameters

Parameter	Hazard ratio (CI)		
	Valaciclovir for 7 days vs acyclovir	Valaciclovir for 14 days vs acyclovir	Valaciclovir for 7 days vs valaciclovir for 14 days
Duration of pain ^a			
Intent to treat	1.34 (1.12–1.60)	1.22 (1.03–1.46)	1.10 (0.92–1.30)
Ophthalmic herpes zoster subset	1.27 (0.72–2.22)	1.15 (0.66–2.00)	1.10 (0.63–1.93)
Duration of abnormal sensations			
Intent to treat	1.18 (0.99–1.41)	1.27 (1.07–1.52)	0.93 (0.78–1.10)
Ophthalmic herpes zoster subset	1.12 (0.60–2.07)	1.36 (0.75–2.47)	0.82 (0.45–1.48)
Time to cessation of new lesion formation			
Intent to treat	1.03 (0.89–1.20)	0.99 (0.85–1.14)	1.05 (0.91–1.21)
Ophthalmic herpes zoster subset	1.27 (0.78–2.05)	1.28 (0.80–2.03)	0.99 (0.63–1.55)
Time to development of $\geq 50\%$ crusting or healing rash			
Intent to treat	1.00 (0.87–1.16)	1.02 (0.88–1.18)	0.98 (0.85–1.14)
Ophthalmic herpes zoster subset	0.95 (0.59–1.53)	1.00 (0.63–1.58)	0.96 (0.60–1.52)

^a Median days to pain cessation: 7-day valaciclovir treatment, 38 days; 14-day valaciclovir treatment, 44 days; acyclovir treatment, 51 days.

ration (Table 3). Gender was not a significant covariate. Treatment beginning within 48 h of rash onset did not influence pain outcome differently from treatment starting from 48 to 72 h of rash onset.

Postherpetic neuralgia. Pain after rash healing occurred in 85% of the patients in the acyclovir group, 79% of the patients in the group receiving valaciclovir for 7 days, and 80% of the patients in the group receiving valaciclovir for 14 days. Treatment with valaciclovir significantly accelerated the resolution of pain that persisted after rash healing compared with treatment with acyclovir (hazard ratio = 1.32, CI = 1.11 to 1.58, and $P = 0.002$ for the 7-day valaciclovir group; hazard ratio = 1.21, CI = 1.02 to 1.44, and $P = 0.03$ for the 14-day valaciclovir group). Pain persisting for more than 30 days after the time of enrollment occurred in 57% of patients in the acyclovir group, 49% of patients in the 7-day valaciclovir group, and 51% of patients in the 14-day valaciclovir group. The median duration of pain after rash healing was 30 days for the 7-day valaciclovir group, 35 days for the 14-day valaciclovir group, and 39 days

for the acyclovir group. Treatment with valaciclovir also accelerated the resolution of pain that persisted for more than 30 days compared with acyclovir (hazard ratio = 1.24, CI = 1.04 to 1.48, and $P = 0.01$ for the 7-day valaciclovir group; hazard ratio = 1.17, CI = 0.98 to 1.39, and $P = 0.09$ for the 14-day valaciclovir group).

Abnormal sensations and pain severity. Both valaciclovir treatments shortened the duration of abnormal sensations compared with acyclovir (Table 2). The median times to the cessation of abnormal sensations were 45 and 38 days for the 7- and 14-day valaciclovir groups, respectively, and 57 days for the acyclovir group. Mean scores (CIs) did not reveal any treatment-related trends for pain intensity or unpleasantness, as determined by use of the Gracely scales in 914 patients in centers in countries where English is the native language.

Pain medication use. Overall, nonnarcotic analgesics were the most commonly used type of medication prescribed to control pain and were used by 76, 75, and 82% of patients randomized to the 7- or 14-day valaciclovir group or the acyclovir group, respectively. Opioids were used by 53, 49, and 53% of patients in these respective treatment groups. Antidepressants were used by 8 to 10% of patients in each treatment group. Use of medications for pain declined progressively over time in each treatment group. The mean \pm standard deviation total analgesic unit dose equivalents were 107.8 ± 191 units for the 7-day valaciclovir group, 88.3 ± 187 units for the 14-day valaciclovir group, and 114.7 ± 218 units for the acyclovir group.

Cutaneous endpoints. Intent-to-treat analysis for cutaneous endpoints showed similar results among the treatment groups (Table 2), with the median times to cessation of new lesion formation (3 days) and to $\geq 50\%$ crusting or healed rash (5 days) being identical in all three groups. Hazard ratios were close to unity for these primary cutaneous efficacy parameters.

Quality of life. Herpes zoster markedly impaired quality of life, as indicated by the pain, sleep, and energy dimensions of the Nottingham Health Profile. Mean scores across all treatment groups at presentation were 36, 40, and 38, respectively, compared with values of 11, 24, and 22, respectively, for age-matched healthy subjects (16). Mean scores for pain, sleep, and energy improved steadily with time, so that normal values were achieved by week 8 (pain, 11; sleep, 20; energy, 21). Mean

TABLE 3. Cox's proportional hazards analysis of factors influencing pain duration

Factor	Hazard ratio (CI)	P value for hazard ratio	Median pain duration (days) ^a
Age, 50–60 vs >60 yr	1.42 (1.20–1.67)	0.0001	31 vs 50
Prodromal pain, absence vs presence	1.30 (1.06–1.56)	0.008	26 vs 49
Pain severity on day 1			
Very mild vs severe	3.00 (2.26–3.99)	0.0001	26 vs 103
Mild vs severe	2.23 (1.69–2.95)	0.0001	36 vs 103
Moderate vs severe	1.58 (1.21–2.06)	0.0007	55 vs 103
Rash onset in relation to treatment initia- tion, ≤ 48 vs 48–72 hr	0.91 (0.79–1.05)	0.207	50 vs 38
Gender, female vs male	0.94 (0.82–1.09)	0.44	51 vs 38

^a Median pain duration derived from Kaplan-Meier analysis with no adjustments for other covariants.

TABLE 4. Adverse events, without regard to causality, reported by at least 3% of patients in one or more treatment groups

Event	No. of occurrences (% patients)		
	Valaciclovir for 7 days (n = 384)	Valaciclovir for 14 days (n = 381)	Acyclovir (n = 376)
Nausea	74 (16)	79 (17)	81 (19)
Headache	50 (11)	70 (14)	54 (13)
Vomiting	42 (9)	19 (4)	30 (8)
Diarrhea	28 (7)	17 (4)	32 (7)
Constipation	21 (5)	21 (6)	21 (5)
Asthenia	15 (4)	23 (5)	22 (5)
Dizziness	17 (4)	15 (4)	25 (6)
Anorexia	11 (3)	12 (3)	10 (3)
Abdominal pain	14 (3)	16 (4)	13 (3)
Dyspepsia	15 (3)	7 (2)	8 (2)

scores (standard error) for pain for the 7- and 14-day valaciclovir groups and the acyclovir group were 19.2 (1.6), 15.5 (1.4), and 20.4 (1.6), respectively, at day 30, and 10.3 (1.2), 10.2 (1.3), and 12.3 (1.3), respectively, at week 8. Although each of these pain scores was higher in the acyclovir group, only for the 14-day valaciclovir group at day 30 was the difference statistically significant.

Ophthalmic herpes zoster subset. Herpes zoster ophthalmicus occurred in 119 (10%) patients, with similar proportions in each treatment group (Table 1). Ocular involvement was present in 34 (29%) patients with ophthalmic herpes zoster at presentation and occurred during the observation period in an additional 17 patients. Twenty-three patients had serious ocular involvement (keratitis, uveitis, iritis, corneal or scleral involvement), and 28 patients had minor ocular involvement (conjunctivitis, "red eye," excessive lacrimation). In >90% of these patients, the ocular involvement resolved within 5 weeks. Hazard ratios for treatment differences for the three primary efficacy variables in the ophthalmic herpes zoster subset were consistent with those of the overall analysis (Table 2).

Complications of herpes zoster. Nonocular complications of

herpes zoster were uncommon in the present study and occurred in approximately 4% of patients overall, with no apparent differences between treatment groups in either numbers or type of complications. Cutaneous complications (secondary bacterial infections, edema, and erosions) were present in 2 patients at presentation and developed during the study in 22 additional patients (1.9% overall). Motor neuropathies, usually manifest as limb weakness or facial paralysis, were evident at presentation in 5 patients and developed during the study in 14 additional patients (1.2% overall). Most cutaneous complications resolved within 10 days, while the average time for resolution of motor neuropathies was 6 weeks. No patients developed central nervous system or visceral organ involvement.

Safety. The adverse experience profiles of the two valaciclovir treatments were very similar to each other and to that of acyclovir. Most adverse experiences were of mild severity. Only nausea and headache were reported by more than 10% of the patients in any group (Table 4). Only one serious adverse experience (severe headache in a 14-day valaciclovir recipient) was considered possibly attributable to study medication. There were no clinically significant differences between treatment groups with regard to the distribution or changes from baseline for any clinical chemistry or hematology parameter. In particular, valaciclovir administration was not associated with changes in renal function. Despite the wide variation in estimated creatinine clearance values at presentation (<20 to >150 $\mu\text{mol/liter}$), valaciclovir and acyclovir treatments were without clinically significant adverse effects.

Plasma acyclovir concentrations and pharmacokinetics. Mean plasma acyclovir concentrations were higher in valaciclovir recipients than in acyclovir recipients (Fig. 2). On the basis of population pharmacokinetic analyses of samples from 1,133 patients, estimated peak acyclovir concentrations for valaciclovir recipients (mean, 5.73 $\mu\text{g/ml}$ [25.2 μM]; range, 2.76 to 16.1 $\mu\text{g/ml}$ [12.3 to 71.5 μM]) were almost three times greater than those for acyclovir-treated patients (mean, 2.23 $\mu\text{g/ml}$ [9.90 μM]; range, 1.0 to 12.6 $\mu\text{g/ml}$ [range, 4.44 to 55.9 μM]). Estimated mean daily area under the plasma concentration-time curve after valaciclovir administration (88.6

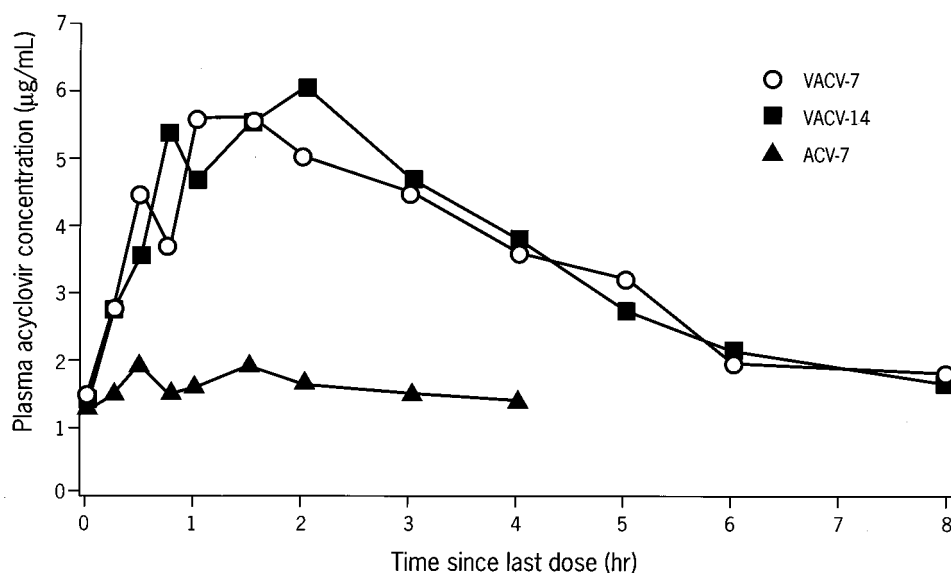


FIG. 2. Plasma acyclovir concentrations during one dosing interval in patients with herpes zoster treated with oral valaciclovir or oral acyclovir. VACV-7, valaciclovir at 1,000 mg three times daily for 7 days; VACV-14, valaciclovir at 1,000 mg three times daily for 14 days; ACV-7, acyclovir at 800 mg five times daily for 7 days.

$\text{h} \cdot \mu\text{g} \cdot \text{h/ml}$; $393 \mu\text{M} \cdot \text{h}$) was more than twice that following oral acyclovir administration ($40.1 \mu\text{g} \cdot \text{h/ml}$; $178 \mu\text{M} \cdot \text{h}$). The estimated bioavailability of acyclovir after oral valaciclovir administration was approximately four times greater than after oral acyclovir administration. The mean plasma elimination half-lives of acyclovir in valaciclovir and acyclovir recipients was 3.4 and 3.5 h, respectively.

DISCUSSION

The study described here was the largest controlled investigation to date of any antiviral agent for the treatment of herpes zoster. It demonstrates that greater systemic acyclovir exposure delivered by valaciclovir results in accelerated resolution of the pain associated with herpes zoster while retaining acyclovir's established safety profile; it confirms that therapy beyond 7 days does not confer additional benefit on herpes zoster-associated pain, and it describes how several pain-related aspects of herpes zoster affect quality of life and how treatment affects these.

Pain is the most debilitating feature of herpes zoster. The majority of patients suffer pain immediately before and during the acute rash phase (5), but a more important clinical challenge is the need to prevent or reduce the possibility of persistent pain. In a number of previous studies, acyclovir was shown to have benefits on chronic herpes zoster-associated pain; when the results were pooled, there was a reduction of more than 50% in pain duration in acyclovir recipients compared with that in placebo recipients and a decrease of between 48 and 86% in the proportion of patients in whom pain persisted for at least 6 months (7, 15). Analysis of the time to complete the cessation of herpes zoster-associated pain in the current study showed an additional benefit of valaciclovir over acyclovir that, on the basis of hazard ratios, was on average between 22 and 34%. Valaciclovir also further reduced, from 26 to 19%, the proportion of patients in whom pain persisted for at least 6 months.

In the present acyclovir-controlled study, persistent pain was evaluated in several ways, and all evaluations consistently demonstrated a superior benefit of treatment with valaciclovir compared with treatment with acyclovir. The principal study endpoint was time to the complete cessation of herpes zoster-associated pain, which demonstrated a significant advantage for both valaciclovir groups by an analysis that incorporates all data throughout the 6-month study period. Results of the analyses of abnormal sensations, analgesic use, the pain dimension of the Nottingham Health Profile, and effects on the duration of pain in the 10% of patients with ophthalmic herpes zoster were consistent with the results for the primary endpoint, herpes zoster-associated pain. The benefit of valaciclovir over that of acyclovir against pain in the ophthalmic herpes zoster subgroup was not expected to attain statistical significance because of small patient numbers.

An additional benefit of valaciclovir compared with acyclovir was also demonstrated for several analyses of postherpetic neuralgia. Evaluation of postherpetic neuralgia is complicated by the lack of a universally accepted definition. By using the definition of either pain after rash healing or pain lasting for more than 30 days, treatment with valaciclovir for 7 days showed a significant advantage over treatment with acyclovir in reducing the duration of postherpetic neuralgia. Treatment with valaciclovir compared with treatment with acyclovir also resulted in a decrease in the proportion of patients with persistent pain at 6 months that was statistically significant for both the 14-day valaciclovir group and the pooled valaciclovir

groups. However, measures of pain severity and quality of life did not detect treatment-related differences.

With the exception of advancing age, no other clinical prognostic features had previously been proven to influence pain outcome following herpes zoster, although some have been suspected. Prodromal pain is thought to result from virus-mediated nerve damage, which has also been implicated in the pathophysiological mechanisms of the development of postherpetic neuralgia (17). Severe pain at presentation and during the acute rash phase has also been suggested as predisposing the patient to the development of prolonged pain (22, 27). With the availability of a large database (1,138 patients), these two features, in addition to age, were shown in the present study to predispose patients to more prolonged pain. In contrast, treatment beginning within 48 to 72 h of rash onset appeared to confer the same benefit as treatment beginning within 48 h.

When the present study began, the optimal treatment duration for maximum clinical benefit against pain was unclear. Some of the placebo-controlled trials of oral acyclovir for the treatment of herpes zoster evaluated 7-day treatment courses, while others examined 10-day treatment courses (11, 14, 18, 28). A controlled trial of acyclovir given for 7 or 21 days was reported recently (27) and demonstrated no significant advantage of 21 days of therapy over 7 days of therapy on the duration of herpes zoster-associated pain. The results for the 14-day valaciclovir group in the current study confirm the observation that no additional benefit is achieved with antiviral treatment for longer than 7 days.

Whether it is administered for 7 or 14 days, valaciclovir had the same safety profile as acyclovir. Previous placebo-controlled trials of oral acyclovir in immunocompetent adults with herpes zoster have shown that adverse events occurred in similar proportions of patients receiving acyclovir and placebo, suggesting that such events are typical features of the disease rather than a result of therapy with acyclovir (14, 18, 28). The results of the present study further support this concept. Safety monitoring, particularly for renal function, was rigorous because acyclovir is excreted principally via the kidney. There were no clinically important changes in serum creatinine values during the 7- or 14-day treatment period, even though renal function at presentation, as estimated from creatinine clearance, spanned the range from <20 to >150 ml/min, as may be expected for a typical patient population with herpes zoster. Although the daily area under the plasma concentration-time curve after oral valaciclovir administration was comparable to that after intravenous acyclovir administration, peak plasma acyclovir concentrations were markedly lower after valaciclovir administration ($5.73 \mu\text{g/ml}$ [$25.2 \mu\text{M}$] versus $20.7 \mu\text{g/ml}$ [$91.9 \mu\text{M}$]) (24), and renal toxicity was therefore not expected.

The present study with a large patient population has demonstrated that valaciclovir offers significant advantages over acyclovir for the treatment of herpes zoster in older adults. Treatment with valaciclovir in a convenient three-times-daily regimen accelerated the resolution of herpes zoster-associated pain and postherpetic neuralgia, reduced the proportion of patients with pain persisting for at least 6 months, and retained the safety profile of acyclovir.

APPENDIX

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